

SUMMARY

The intracarotid infusion of hyperosmolar sucrose solutions such as 30% is widely used to temporarily open the blood-brain barrier in control animal species. In the present study, an attempt was made to analyze the hemodynamic changes caused by the intracarotid infusion with special reference to possible metabolic disturbances in the brain. The cerebral blood flow is reflected by the cerebral venous outflow rate, intracranial pressure, arterial blood pressure and cardiac output were continuously recorded during and following the infusion. It was

HEMODYNAMIC CHANGES IN BRAIN CAUSED BY LOCAL INFUSION OF HYPEROSMOLAR SOLUTIONS, IN PARTICULAR RELATION TO BLOOD-BRAIN BARRIER OPENING

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SUMMARY

The intracarotid infusion of hyperosmolar aqueous solutions such as urea is widely used to transiently open the blood-brain barrier in various animal species. In the present study in the rat an attempt was made to analyze the hemodynamic changes caused by the intracarotid infusions with special reference to possible mechanisms underlying the barrier opening. The cerebral blood flow - as reflected by the cerebral venous outflow rate -, intracranial pressure, intracarotid pressure and systemic blood pressure were continuously measured during and following the infusions. It was found that intracarotid infusions of hyperosmolar solutions induce cerebral vasodilatation and flow increase. Autoregulation is impaired. Probably, a direct vasodilator mechanism is involved, but, depending on volume and osmolarity of the solution used, the changes may be heavily influenced by vascular distension due to intracarotid pressure effect, and by systemic pressure changes. All these mechanisms can contribute to blood-brain barrier opening. The local vasomotor and systemic effects of a hyperosmolar solution of urea, capable of opening the barrier, are not normalized until about 6 min after the administration.

The intracerebral infusion of hyperosmolar solutions such as urea is

widely used to transiently open the blood-brain barrier in various animal species.

In the present study in the rat an attempt was made to analyze the hemodynamic

changes caused by the intracerebral infusion with special reference to possible mech-

anisms underlying the barrier opening. The cerebral blood flow - as reflected by the

cerebral venous outflow rate - intracranial pressure, intracerebral pressure and systemic

blood pressure were continuously measured during and following the infusion. It was

found that intracerebral infusion of hyperosmolar solutions induces cerebral vasodilation

and flow increases. Autoregulation is impaired. Probably, a direct vasodilator mechanism

is involved, but, depending on volume and osmolarity of the solution used, the changes

may be partly influenced by vascular distension due to intracranial pressure effect,

and by systemic pressure changes. All these mechanisms can contribute to blood-brain

barrier opening. The local vasomotor and systemic effects of a hyperosmolar solution

of urea, capable of crossing the barrier, are not normalized until about 6 min after the

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INTRODUCTION

Intracarotid infusion of hyperosmolar solutions of e.g. urea or lactamide has been widely used for transient opening of the blood-brain barrier, thus permitting the passage into the brain of a variety of molecules including such as horse-radish peroxidase (mol wt = 40.000) and albumin (60.000)^{3,7,19,20,21,23}. It has been suggested that the hyperosmolar solutions cause shrinkage of endothelial cells, which is believed to open the barrier at the tight junctions between contiguous endothelial cells³. However, this may not be the only mechanism responsible for the barrier opening. It has been shown that hyperosmolar solutions cause relaxation of vascular smooth muscle in various vascular beds including the cerebral circulation^{4,12,14, 18, 22, 25}. Further, a rapid infusion of solutions may have a direct pressure effect causing vascular distension and change blood viscosity, hence affecting the blood flow². In the present study an attempt was made to analyze the hemodynamic changes caused by intracarotid infusions with special reference to possible mechanisms underlying the blood-brain barrier opening.

METHODS

Preparation of animals

The experiments were performed on male rats (300–350 g; of the Wistar strain for determination of cerebral blood flow, Sprague-Dawley rats for blood-brain barrier studies) that had free access to pellet food and tap water until operation. Anesthesia was induced with 2–3% halothane to allow tracheotomy and immobilization with tubocurarine chloride (1mg/kg i.v.). The animals were artificially ventilated on 70% N₂O and 30% O₂ (Braun), the PaCO₂ being adjusted to about 35 mm Hg. Halothane 0.6–0.8% was given during the operation procedure, then withdrawn. The body temperature was kept at 37°C by means of intermittent heating.

Cerebral blood flow

In 6 animals catheters were placed just distal to the aortic bifurcation via the femoral artery on one side for recording of the systemic blood pressure via a pressure transducer (Elema, Sweden) and sampling of arterial blood for blood gas measurements (BMS Mk II; Radiometer, Copenhagen). One femoral vein was cannulated for infusion of fresh donor blood during the period of blood sampling. After ligation of its branches, the main trunks of both external carotid arteries were cannulated centripetally with the catheter opening

placed within one mm distal to the carotid bifurcation. Injections through the catheter in the external carotid were thus carried into the internal carotid artery, supplying the forebrain (though in addition to the territory of the pterygopalatine and occipital arteries). The intracranial pressure (ICP) was estimated through a needle inserted into the cisterna magna, connected to a pressure transducer (Elema).

Determination of cerebral blood flow (CBF) was performed by the technique developed by Nilsson and Siesjö^{16,17} with sampling of cerebral venous blood from the retroglennoid vein on one side. Thus, the cerebral venous outflow was measured by drop counting in a closed circuit diverting blood from one retroglennoid vein, during compression of the contralateral vein, and returning the blood through a catheter in the external jugular vein on one side into the central venous system. The outflow volume was calculated by the use of a diagram relating drop rate to volume (drop volume increasing from 30 $\mu\text{l}/\text{drop}$ to 42 $\mu\text{l}/\text{drop}$ when cerebral venous outflow increased from subnormal values to 6–8 times normal). It was controlled that hemodilution up to 40% (volume) with Krebs–Ringer buffer solution or urea at a concentration of 5 M dissolved in blood (which may distort blood corpuscles and hence affect hematocrit values and blood viscosity), did not increase the drop volume more than 5 per cent. Hence no attempts were made to correct for the possible influence upon drop volume of infused solutions².

The outflow volume was converted into CBF values expressed in $\text{ml}/100 \text{ g} \times \text{min}$ by measurement of the cerebral arterio-venous difference in oxygen content (AVDO_2) in the control situation. Assuming a cerebral oxygen consumption (CMRO_2) of $7.58 \text{ ml}/100 \text{ g} \times \text{min}$ ¹⁶, the CBF (in $\text{ml}/100 \text{ g} \times \text{min}$) could be calculated from 7.58 and related to the actual venous outflow volume. The cerebrovascular resistance (CVR) = $\frac{\text{AoP} - \text{ICP}}{\text{CBF}}$.

The effect on the CBF, as reflected in the cerebral venous outflow rate, as well as the effect on intracranial pressure, was recorded following simultaneous infusion into each internal carotid artery of 50 μl during 10 sec, 250 μl during 15 sec, or 1 ml during 15 sec of Krebs–Ringer buffer solution or blood, with or without addition of urea (to a final concentration in the infusate of 0.5, 1.0, 2.0, 3.5 or 5.0 M) or mannitol (0.5 or 1.0 M). Several experiments were run in each animal, but a new experiment was not undertaken until the venous outflow rate had returned to control levels. Experiments were only undertaken as long as an adequate reactivity of the cerebral blood flow to hypercapnia was found.

Intracarotid pressure

In one group of animals (4 rats) a needle was inserted into the external carotid catheter on one side, with the opening placed just distal to the carotid bifurcation. The outer diameter of the needle was 0.3 mm as compared to the inner diameter of the catheter, 0.5 mm; this allows a free flow past the needle during the infusions. In addition, a catheter was placed into one femoral artery for recording of systemic blood pressure and sampling of arterial blood for blood gas measurements. These animals were used solely to measure the effect on intracarotid pressure (CarP) during the various intracarotid infusions (50 μ l/10 sec, 250 μ l/15 sec and 1 ml/15 sec).

Blood-brain barrier permeability

In 40 animals, catheters were placed in one femoral artery (for blood pressure recording and sampling of blood) and in one femoral vein (for infusion of Evans blue). Evans blue binds with serum proteins and does not therefore penetrate the blood-brain barrier under normal conditions. The right external carotid artery was cannulated as described above. Evans blue (1 ml of a 1.5–2.0% solution in Krebs–Ringer buffer) was slowly infused 10–20 min before an intracarotid infusion of urea, dissolved in Krebs–Ringer buffer solution (2.0, 3.5 or 5.0 M urea in 50 μ l infused during 10 sec; 2.0, 3.5, or 5.0 M urea in 250 μ l infused during 15 sec; 2.0 or 3.5 M urea in 1 ml infused during 15 sec). In one group of animals 1 ml of the buffered solvent alone was infused during 15 sec. After a further 10 min the animals were killed by perfusion with 0.9% saline followed by 10% neutral formaline through the left ventricle of the heart, for macroscopic and fluorescence microscopic examination of extravasation of Evans blue in the brain. The Evans blue–albumin complex displays a red fluorescence under the fluorescence microscopic conditions used (Hg lamp, HBO 200; primary filter, BG 12; secondary filter, OG 4).

RESULTS AND COMMENTS

Cerebral blood flow and intracranial pressure

The resting mean aortic blood pressure (AoP) was 118 ± 3 mm Hg, resting ICP 12.3 ± 0.9 mm Hg, CBF 77.9 ± 2.6 ml/100 g $\times$ min, $AVDO_2$ 9.82 ± 0.32 ml/100 ml, PaO_2 101.8 ± 2.5 mm Hg, $PaCO_2$ 36.5 ± 0.9 mm Hg and pH 7.332 ± 0.135 (mean $\pm$ SEM). The effects of intracarotid infusions are illustrated in Fig. 1 and 2, showing data of representative experiments. Infusion of 50 μ l of Krebs–Ringer solution during 10 sec

(Fig. 1) induced a slight increase in CarP and CBF, and a very small change in ICP. AoP was unchanged. The same volume of buffer solution with 5 M urea added gave rise to a pronounced and prolonged increase in CBF and ICP, but also, with a time lag of 2-3 sec, an increase in AoP. During this period the change in CBF essentially paralleled the AoP increase. Infusion of 1 ml of buffer solution during 15 sec induced an immediate increase in CarP, AoP, CBF and ICP. This volume of hypertonic solution (2 M urea) exaggerated and prolonged these changes: for example, the CBF had not returned to a resting level until 6 min later. A shortlasting cardiac arrhythmia began 7 sec after the start of infusion, causing a transient fall in AoP. Data of the whole material are summarized in table I. Infusion of 250 μ l buffer solution in 15 sec caused changes ranking in between those of 50 μ l/10 sec and 1 ml/15 sec. Increasing hyperosmolarity of 50 μ l/10 sec infusions increased the degree and duration of AoP, CBF and ICP changes. In the lower part of table I the effects of using blood instead of buffer solutions are shown. The CBF changes were less pronounced, evidently due to absence of hemodilution, while the effects upon CarP, AoP and also ICP were similar to those induced with buffer solution. With addition of urea to blood the changes in AoP, CBF and ICP were pronounced seemingly even more so than when similar concentrations of urea was used in buffer solution, probably due to the fact that the effective plasma concentration was higher than the concentration figures given.

Blood-brain barrier permeability

All brain regions taken from animals injected with Evans blue, but not treated with urea to induce opening of the blood-brain barrier, showed no macroscopically visible staining of the parenchyma. No Evans blue could be found in the vascular walls except for a red fluorescence restricted to the intima of the pial vessels. Under conditions when the barrier was opened (see table II), a blue staining with a varying localization in individual animals was seen macroscopically in superficial as well as deep structures of the hemisphere of the injected side and in the territory of the anterior cerebral artery in the contralateral hemisphere. The extravasation of Evans blue corresponded to the regions reached by the initial high concentration of urea (the anterior cerebral artery is unpaired, which means that a substance injected into one carotid artery reaches the territory of this artery in both hemispheres essentially undiluted). In a few animals the ipsilateral hemisphere of the cerebellum was stained, which indicates that the

infusion had caused a transient change in flow distribution to the vertebrobasilar territory.

In the fluorescence microscope, a red fluorescence of patchy distribution was seen extracellularly in all parts of the parenchyma and in the vessel walls in the regions showing a macroscopically visible staining. The leakage was particularly evident at the level of small arterioles, capillaries and veins. Sometimes also the neurons were seen to be loaded with red-fluorescent material. Occasionally, a red fluorescence was also observed in the wall of parenchymal vessels outside areas showing macroscopic extravasation, and sometimes in the wall of pial arteries and arterioles. In animals without macroscopically visible extravasation of Evans blue no signs of barrier damage appeared in the fluorescence microscope.

With an increase in the volume and rate of infusion it was possible to achieve the same degree of barrier opening with a lower concentration of urea in the infusate (table II, fig. 3 A and B), indicating a continued volume and osmolarity mechanism of the barrier opening.

DISCUSSION

The results indicate that several factors influence CBF when hypertonic solutions are given by intracarotid injection. Thus, evidently urea or mannitol per se caused an increase in CBF, but the effect was modulated by the volume and type of carrier solute used, and by the changes in systemic blood pressure. On the basis of these conditions it has been possible to interpret some of the mechanisms that may be responsible for the blood-brain barrier opening.

An intracarotid infusion of a volume of 1 ml during 15 seconds in the rat corresponds to a flow rate that is probably more than 5 times normal internal carotid blood flow (which is about 10 μ l/sec, equivalent to 80 ml/100 g $\times$ min¹⁶ for a 0.75 g brain hemisphere). Therefore, it was not surprising to find that an intracarotid infusion of this amount of blood caused a mean increase in CBF to 144%; the corresponding elevation with Krebs-Ringer buffer solution instead of blood was to 382%. It is conceivable that not all of the infused volume reaches the brain circulation. At this high infusion rate, with the infusion directed downstream into the common carotid, it is most probable that part of the infusate does not enter the internal carotid but instead reaches the innominate artery and aorta. Further, only part of the infused volume enters the cerebral circulation, since

the internal carotid branches off into the pterygopalatine artery extracranially. When 250 μ l was infused during 15 sec into the internal carotid the cortical blood flow was increased to 134 and 204% with blood and buffer solution, respectively. Even the infusion of 50 μ l during 10 seconds caused a minor increase in cortical blood flow (to 111 and 125% with blood and buffer solution, respectively). It is suggested that the volume of carrier solvent injected may in itself markedly affect the cerebral hemodynamics by vascular distension unless adjusted to volumes representing only fractions of the actual internal carotid flow. Also the volume induced systemic blood pressure effects have to be taken into account. It is notable that an infusion into the rabbit internal carotid artery of a solute of 5 ml during 25–30 sec, as used by Rapoport *et al.*²⁰ should mean a flow rate that exceeds the normal hemispheric blood flow by about 4 times.

The use of Krebs–Ringer buffer solution gave rise to a more pronounced flow increase than when blood was infused. This effect was evidently due to hemodilution and lowering of the blood viscosity. The increase in ICP was similar in both situations indicating that the same degree of vasodilatation and increase of intracranial blood volume occurred.

The increase in CBF by concentrations of urea or mannitol at or above 0.5 M was markedly higher than that obtained by an infusion of the same volume of buffer solution alone. An augmented flow was also obtained when blood was substituted for the buffered solution as infusate. There are several possible explanations for this effect of hypertonic solutions:

First, the systemic blood pressure reaction has to be taken into account. Thus, urea and mannitol both caused a transient increase in systemic blood pressure and CBF. Normally, CBF remains relatively constant ("autoregulation") over a wide range of cerebral perfusion pressure induced by changes in systemic arterial pressure⁸. The present finding that the long-lasting increase in CBF obtained by the hyperosmolar solutions almost paralleled the increase in AoP indicates a reduced ability of the brain vessels to compensate for the change in cerebral perfusion pressure, *i.e.* to autoregulate. Fig. 4 shows this relation. However, although a pressure-passive elastic system is indicated, the increase in CBF induced by hypertonic solutions probably involves other mechanisms. Thus, the increase in CBF preceded the increase in AoP (fig. 1). Furthermore, the CBF increase shown in fig. 4 is probably steeper, especially at higher concentrations of urea, than would be expected in a purely pressure-passive elastic system. We conclude that hypertonic solutions have a direct vasodilator effect. It should be noted that also topical application onto pial vessels of hyperosmolar solutions causes vasodilatation²⁵ and barrier damage (extravasation of

Evans blue²⁰).

The mechanism of the vasodilatation is unclear²⁵. It has been suggested that hyperosmolarity may cause local tonic changes, which can affect cerebrovascular tone. Thus, it has been found that hyperosmolar solutions cause a decrease in cellular volume, increase of intracellular K^+ concentration, and hyperpolarization, which all should decrease excitability^{5,24}.

Cerebrovascular resistance is also influenced by factors involving local metabolic mechanisms. However, no consistent change in $CMRO_2$ or cerebral glucose consumption has been reported, as measured several minutes after an infusion of urea¹⁹ or mannitol¹². The electroencephalogram is unaffected 15 sec after the urea infusion¹⁹. It might be added that infusion of a buffer solution displacing blood could induce a shortlasting tissue hypoxia and vasodilatation. However, this mechanism seems less important, since even pronounced hemodilution is compensated for by the increase in flow, possibly elicited by the decreased blood viscosity².

The increase in AoP induced by hyperosmolar solutions is of central origin and probably mediated via a stimulation of sympathetic mechanisms¹⁵. That this effect is not of peripheral origin, i.e. resulting from the increase in circulating plasma volume, is further supported by the fact that an intravenous injection of 5 M urea in 50 μ l or 2 M urea in 1 ml buffer solution did not cause any substantial increase in AoP.

In the present study all infusions were made in a retrograde manner via the external carotid system, leaving the common and internal carotid arteries intact. The technique used by Rapoport and co-workers²⁰ involves temporary or permanent occlusion of the common carotid artery, which in itself may lead to autoregulatory vasodilatation in the cerebrovascular bed, probably increasing vulnerability to mechanical vasodistension stimuli. Manipulation with the common or internal carotid artery may also result in vasoplasm.

In conclusion, intracarotid infusions of hyperosmolar solutions induce cerebral vasodilatation and flow increase. Probably, a direct vasodilator mechanism is involved, but the changes may be heavily influenced by vascular distension due to intracarotid pressure effect, and by systemic blood pressure changes. In addition, hemodilution may increase flow.

The intracarotid infusion of Krebs-Ringer buffer solution alone at the highest infusion rate used (1 ml during 15 sec) did not in itself cause any extravasation of

Evans blue - albumin complex. This indicates that neither this rise in intraluminal pressure nor the flow increase induced by hemodilution produced any barrier damage. In a previous study it was found that an intracarotid infusion of 1 ml of a 2 M solution of urea (in Krebs-Ringer buffer solution) during 15 seconds resulted in a transient opening of the blood-brain barrier in the rat, especially at the level of cerebral microvessels as evidenced by extravasation of Evans blue⁷. Animals receiving 1.5 M urea showed no extravasation, whereas a more marked extravasation was obtained after 3 M urea. A similar threshold concentration of urea infused at 5 ml/25-30 sec was found to cause blood-brain barrier opening in the rabbit²⁰. In the present study, when infusing 250 μ l during 15 seconds of a solution of increasing concentrations of urea dissolved as above, no extravasation could be obtained until the concentration was raised to 3.5 M. At the lowest infusion rate (50 μ l during 10 sec), 5 M urea induced a barrier opening of moderate severity; with 3.5 M urea only a few animals showed any macro- or microscopically detectable signs of barrier damage, and the damage was minor. This clearly indicates that the flow increase caused by the infusion at high rate - although ineffective by itself to disrupt the barrier - contributes to the barrier opening seen with 2 M urea. In the baboon this factor seems to be somewhat less important. Thus, in the experiments by Harper and MacKenzie⁹ a 2 M solution of urea infused at a rate that did not increase the intracarotid pressure more than 10 mm Hg opened the barrier as judged by extravasation of Evans blue.

An increased transendothelial pinocytosis, together with a formation of channels in the endothelial cytoplasm, has been shown to comprise the barrier opening in acute hypertension⁶. The reversibility of the opening is probably related to a pressure-forced overdistension of the vessels along the vascular tree. The blood-brain barrier damage in epileptic seizures is caused by a combined vasodilatation and elevated blood pressure¹¹. Also in this situation an increased pinocytosis has been observed¹. The barrier opening obtained by hyperosmolar solutions was originally suggested to be due to cell shrinkage and opening of tight junctions between contiguous endothelial cells. Studies revealed accumulation of extravasated horse-radish peroxidase between adjacent endothelial cells and in the basal membrane³. However, no opened tight junctions have actually been observed, which indicates that the peroxidase might have reached these locations by transendothelial pinocytosis. This is supported by findings by H.-A. Hansson, J. Holmgren and B. Johansson (to be published). Thus, although the basic significance and

mechanism of endothelial pinocytosis remains to be elucidated, it may be suggested that the increased transendothelial pinocytosis under these experimental conditions is a uniform reaction to the marked dilatation and/or distension in the brain vessels. The present data do not exclude that the barrier opening induced by a hyperosmolar solution such as urea may be partly due to a specific effect upon endothelial cells causing shrinkage resulting in an opening of tight junctions, as initially proposed³. However, from the present results it appears evident that an opening may also occur as a result of vasodilatation and vascular distension. Blocking the increase in blood pressure will minimize the urea-induced barrier opening (Hardebo, to be published). The additional increase in CBF due to a lowered blood viscosity is unlikely to influence blood-brain barrier permeability.

The intracarotid administration of urea is a useful method to open the blood-brain barrier in the study of agents that are normally limited from entering the brain. However, the direct vasomotor effects of urea have to be taken into account. Thus, if vasomotor effects in the brain of various agents are to be studied, these should not be administered until 5-10 min after the urea infusion, when the urea-induced local vasomotor and systemic effects are normalized but the barrier is still open (although to a less extent than during or shortly after the urea infusion; Hardebo, to be published). Urea (2 M in 7-15 ml of a buffered solution, infused over 5-15 sec) has no effect on blood flow, metabolism or physiological reactivity of the cerebral circulation in the baboon 5 min after administration¹⁹ or in the dog (4 M in 20 ml over 15 sec) 10 min afterwards (D. Barry, E.T. MacKenzie and D. Yudilevich, unpublished observations). Similarly, in the present study in the rat, cerebral blood flow and systemic effects are normalized 6 min after administration (2 M urea in 1 ml of a buffered solution over 15 sec). Further, no cerebral edema is noticed after the barrier has been opened by urea¹⁹ or lactamide²¹.

Intravenous infusion of urea is widely used in the acute treatment of raised intracranial pressure. However, the present finding of an almost instantaneous and marked dilatation of cerebral vessels and the concomitant increase in intracranial pressure, as well as the prominent effects on systemic blood pressure suggests the risk of an initially adverse effect unless the infusion is initiated slowly (cf. ref.¹⁰). On the other hand, it is highly unlikely that the systemic infusion of urea under clinical conditions, the concentration used and the infusion rate will have any effect on blood-brain barrier permeability.

ACKNOWLEDGEMENTS

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Legends to figures

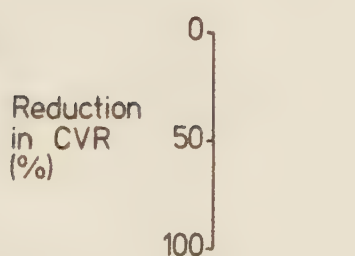
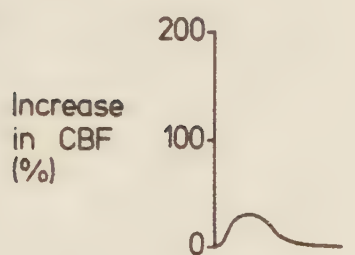
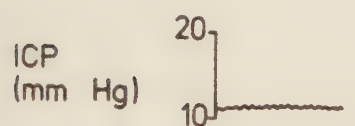
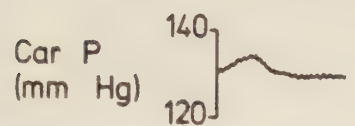
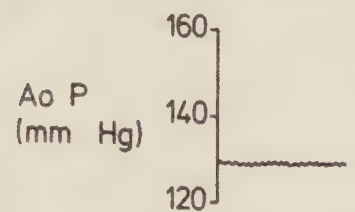
Fig. 1. Representative experiment performed in one animal (intracarotid pressure was measured in a separate animal), illustrating changes in cerebral blood flow (CBF; as reflected by the cerebral venous outflow rate), cerebrovascular resistance (CVR), intracranial pressure (ICP; measured in the cisterna magna), intracarotid pressure measured at the level of the carotid bifurcation (CarP) and aortic (systemic) blood pressure measured via the femoral artery (AoP) induced by an infusion during 10 sec into the internal carotid on both sides of 50 μ l of Krebs-Ringer buffer solution alone or with addition of urea (to a concentration of 5 M in the infusate).

Fig. 2. Representative experiment performed in one animal (intracarotid pressure was measured in a separate animal) illustrating changes in cerebral blood flow (CBF), cerebrovascular resistance (CVR), intracranial pressure (ICP), intracarotid pressure (CarP) and aortic systemic blood pressure measured via the femoral artery (AoP) caused by an infusion during 15 sec into each internal carotid artery of 1 ml of Krebs-Ringer buffer solution alone or with addition of urea (to a concentration in the infusate of 2 M).

Fig. 3. Representative samples of rat's brain removed 10 min after injection of urea into the right carotid artery. 5 M urea in 50 μ l of buffered solute infused over 10 sec induced a moderate blood-brain barrier opening (A), whereas 3.5 M urea in 1 ml infused over 15 sec induced a marked barrier opening (B).

Fig. 4. Changes in perfusion pressure ($PP = AoP - ICP$) and cerebral blood flow (CBF) induced by bilateral intracarotid infusion of $2 \times 50 \mu$ l/10 sec of Krebs-Ringer solution (●) with urea (0.5, 1.0, 3.5 or 5.0 M) added (⊙), or blood (●) with urea (0.5 or 1.0 M) added (⊙). The CBF increase shown after urea is probably steeper than would be expected in a purely pressure-passive elastic system. The thin line indicates the relation in a pressure-passive, rigid system.

Intracarotid infusion of
50 μ l buffer solution/10 sec

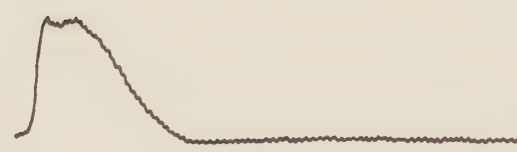


Infusion 

Time
(sec)

0 30

Intracarotid infusion of 5 M urea
in 50 μ l buffer solution/10 sec

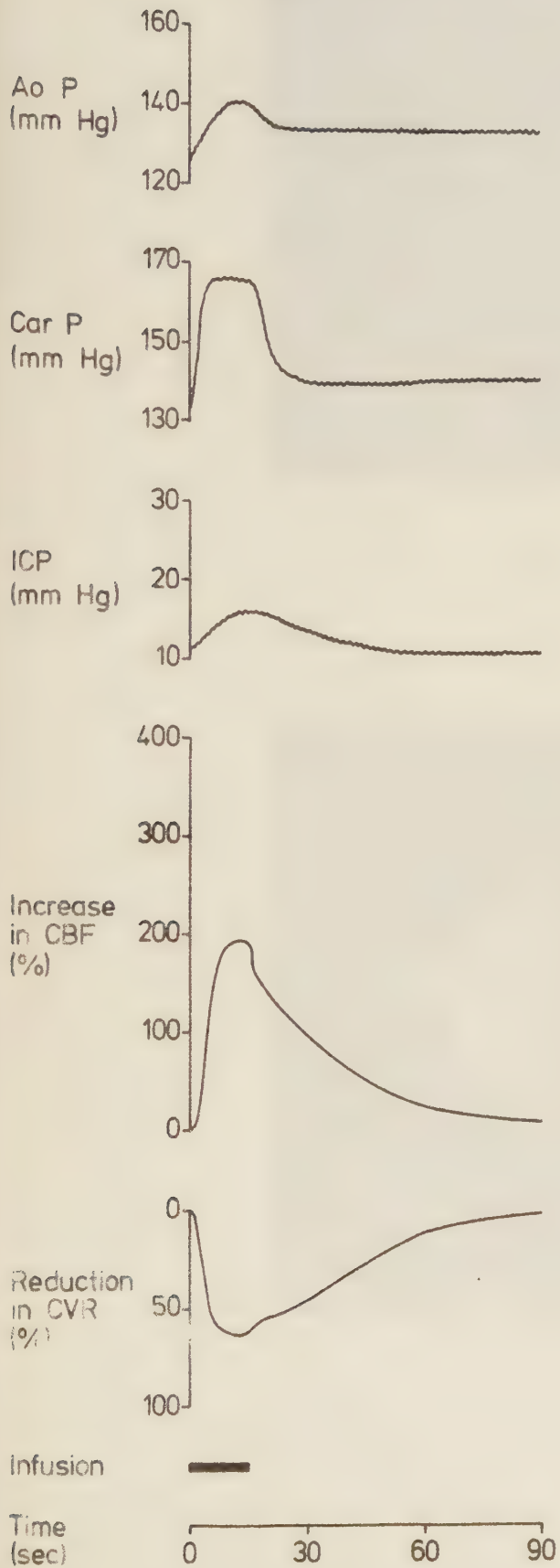


Infusion 

Time
(sec)

0 30 60 90 120

Intracarotid infusion of
1 ml buffer solution / 15 sec



Intracarotid infusion of 2 M urea
in 1 ml buffer solution / 15 sec





Fig. 3 A

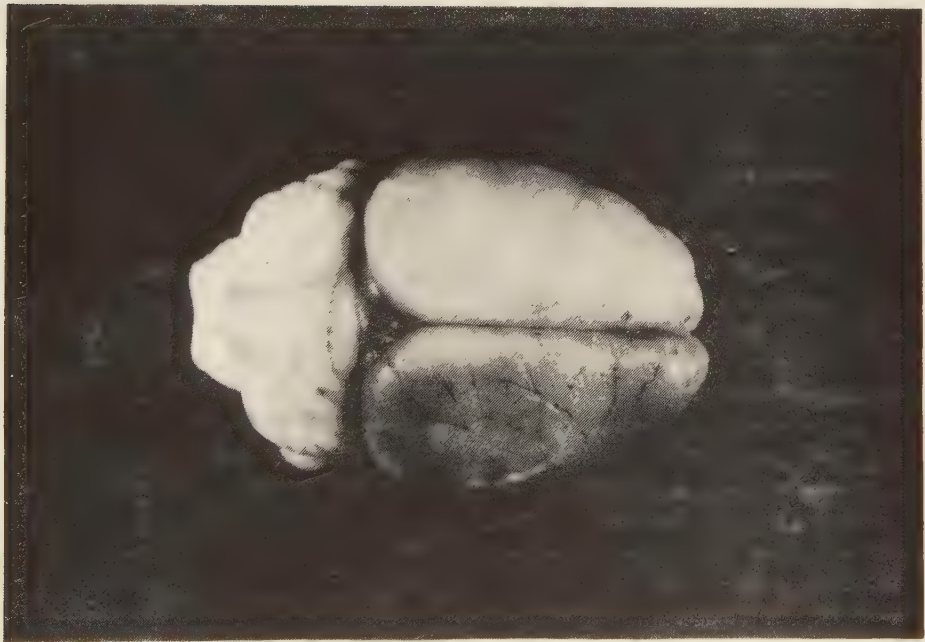


Fig. 3 B

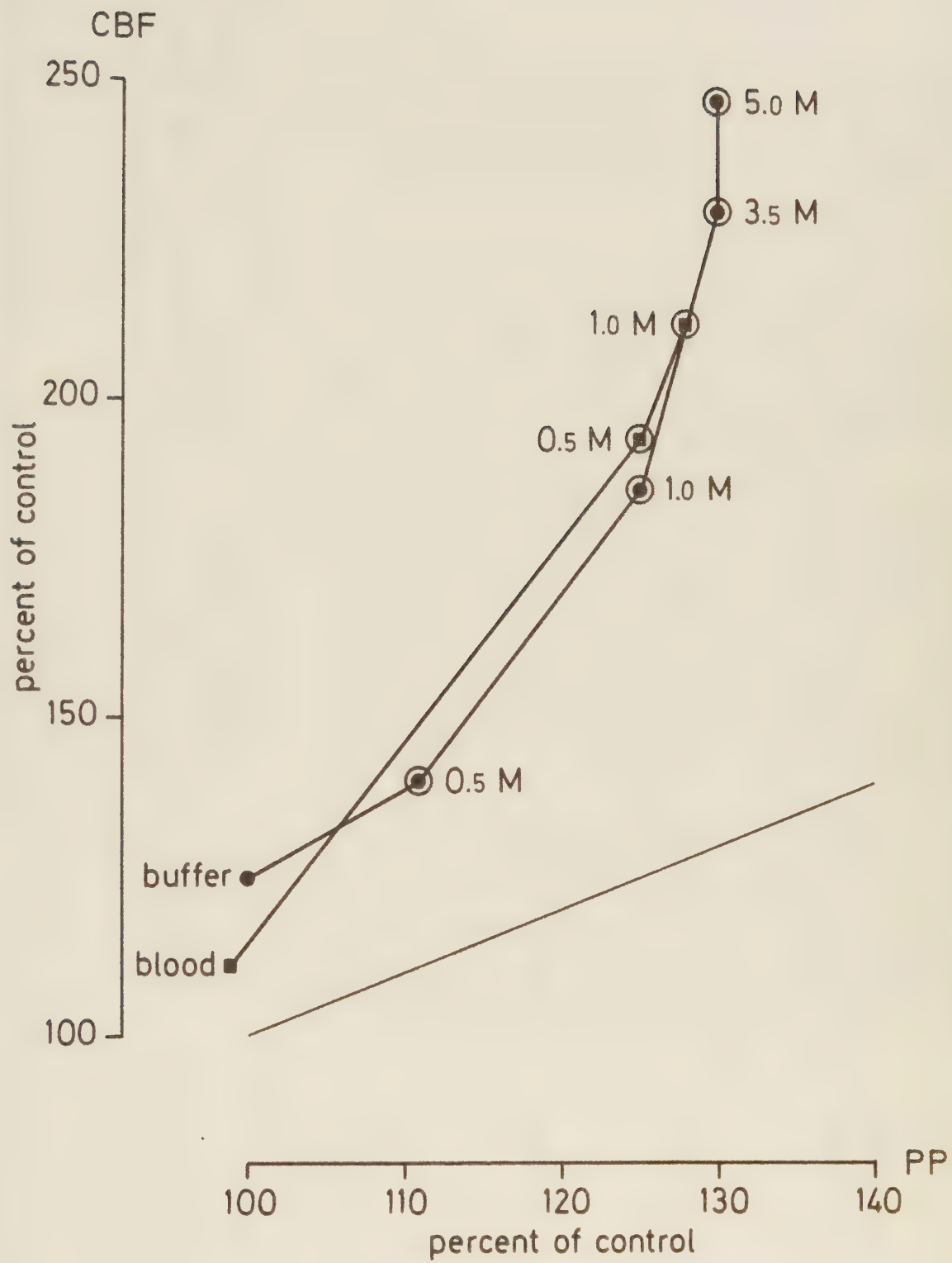


Table 1. Changes in CBF (cerebral blood flow), ICP (intracranial pressure), CarP (carotid pressure) and AoP (aortic pressure) induced by a bilateral intracarotid infusion during 10-15 sec of 50, 250 μ l or 1 ml of Krebs-Ringer buffer solution or blood, with or without addition of urea (0.5 - 5.0 M) or mannitol (0.5 - 1.0 M). A "plateau" increase in CBF was obtained 5-10 sec after the start of infusion, followed by a phase of decay. AoP increase after buffer solution alone simply reflects a transfer along the arterial vascular tree of the increase in intraluminal pressure, caused by the infusion; after addition of urea or mannitol the maximum increase in AoP occurred after the infusion was completed. Mean $\pm$ SEM; (n) = number of observations; 1-2 observations in each animal.

Bilateral intracarotid infusion of		Maximum increase in CBF (%)	Duration of increase in CBF (sec)		Maximum increase in ICP (%)	Maximum increase in AoP (mm Hg)	Maximum increase in CarP (mm Hg)
Buffer solution			"Plateau"	Decay			
50 μ l/10 sec		25.2 $\pm$	3.1 (6)	8.5 $\pm$ 1.1	7.0 $\pm$ 1.5	1.6 $\pm$ 0.7	2.9 $\pm$ 0.3 (10)
- "	with 0.5 M urea	40.3 $\pm$	5.6 (7)	9.3 $\pm$ 0.8	15.1 $\pm$ 1.8	7.5 $\pm$ 1.4	13.0 $\pm$ 1.2
- "	" 1.0 M "	86.6 $\pm$	8.4 (5)	14.4 $\pm$ 0.7	27.2 $\pm$ 3.4	22.5 $\pm$ 2.5	29.0 $\pm$ 1.9
- "	" 3.5 M "	130.5 $\pm$	6.4 (4)	17.0 $\pm$ 1.2	59.3 $\pm$ 2.1	38.3 $\pm$ 1.7	37.0 $\pm$ 1.2
- "	" 5.0 M "	147.5 $\pm$	9.1 (6)	17.3 $\pm$ 0.7	84.0 $\pm$ 4.3	46.8 $\pm$ 2.7	36.7 $\pm$ 3.1
- "	" 0.5 M mannitol	26.0 $\pm$	4.2 (3)	9.7 $\pm$ 2.1	18.7 $\pm$ 0.7	6.7 $\pm$ 1.7	6.0 $\pm$ 1.0
- "	" 1.0 M "	51.6 $\pm$	6.0 (5)	13.8 $\pm$ 1.0	20.2 $\pm$ 1.0	11.0 $\pm$ 1.0	21.0 $\pm$ 1.9
250 μ l/15 sec		103.7 $\pm$	5.4 (7)	16.9 $\pm$ 1.8	18.4 $\pm$ 1.4	16.0 $\pm$ 1.4	11.9 $\pm$ 1.1
1 ml/15 sec		281.8 $\pm$	14.5 (4)	15.3 $\pm$ 2.1	105.0 $\pm$ 9.6	34.0 $\pm$ 3.8	20.5 $\pm$ 3.3
- "	with 2.0 M urea	409.0 $\pm$	9.8 (4)	50.8 $\pm$ 3.9	308.8 $\pm$ 6.9	142.5 $\pm$ 7.8	44.5 $\pm$ 3.2
							12.6 $\pm$ 1.2 (13)
							34.6 $\pm$ 3.7 (5)
Blood							
50 μ l/10 sec		10.8 $\pm$	1.5 (4)	6.5 $\pm$ 0.6	7.3 $\pm$ 1.3	2.0 $\pm$ 0.4	0
- "	with 0.5 M urea	94.0 $\pm$	19.3 (3)	10.3 $\pm$ 0.9	15.3 $\pm$ 0.3	28.3 $\pm$ 4.4	29.7 $\pm$ 3.5
- "	" 1.0 M urea	119,106	(2)	15,15	15,15	39,30	35,27
250 μ l/15 sec		33.6 $\pm$	6.8 (5)	14.4 $\pm$ 0.4	17.2 $\pm$ 2.2	17.3 $\pm$ 1.5	12.0 $\pm$ 1.7
1 ml/15 sec		44.2 $\pm$	4.5 (6)	16.3 $\pm$ 1.6	96.7 $\pm$ 5.4	31.5 $\pm$ 2.5	16.7 $\pm$ 0.8
							29.4 $\pm$ 1.7 (5)

Table II. The incidence of blood-brain barrier lesions, as evidence by extravasation of Evans blue-albumin complex, at various infusion rates with urea, present in the infusate at increasing concentrations. The degrees of extravasation are estimated visually: 0 = no extravasation, + = slight leakage, extravasation in < 10 small areas, ++ = moderate leakage (as illustrated in fig. 3 A), +++ = marked leakage (as illustrated in fig. 3 B).

Infusion rate	Urea conc.	n	Blood-brain barrier lesions			
			+++	++	+	0
50 μ l/10 sec	2.0 M	4				4
	3.5 M	4			2	2
	5.0 M	4		3	1	
250 μ l/15 sec	2.0 M	4				4
	3.5 M	6		2	4	
	5.0 M	3	1	2		
1 ml/15 sec	0.0 M	4				4
	2.0 M	7		5	2	
	3.5 M	4	4			

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